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1: J Immunol. 2003 May 1;170(9):4441-9.

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A pyrazole derivative, YM-58483, potently inhibits store-operated sustained Ca^{2+} influx and IL-2 production in T lymphocytes.

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In nonexcitable cells, Ca^{2+} entry is mediated predominantly through the store depletion-dependent Ca^{2+} channels called store-operated Ca^{2+} (SOC) or Ca^{2+} release-activated Ca^{2+} channels. YM-58483, a pyrazole derivative, inhibited an anti-CD3 mAb-induced sustained Ca^{2+} influx in acute T cell leukemia, Jurkat cells. But it did not affect an anti-CD3 mAb-induced transient intracellular Ca^{2+} increase in Ca^{2+} -free medium, nor anti-CD3 mAb-induced phosphorylation of phospholipase Cgamma1. It was suggested that YM-58483 inhibited Ca^{2+} influx through SOC channels without affecting the TCR signal transduction cascade. Furthermore, YM-58483 inhibited thapsigargin-induced sustained Ca^{2+} influx with an IC_{50} value of 100 nM without affecting membrane potential. YM-58483 inhibited by 30-fold the Ca^{2+} influx through SOC channels compared with voltage-operated Ca^{2+} channels, while econazole inhibited both SOC channels and voltage-operated Ca^{2+} channels with an equivalent range of IC_{50} values. YM-58483 potently inhibited IL-2 production and NF-AT-driven promoter activity, but not AP-1-driven promoter activity in Jurkat cells. Moreover, this compound inhibited delayed-type hypersensitivity in mice with an ED_{50} of 1.1 mg/kg. Therefore, we concluded that YM-58483 was a novel store-operated Ca^{2+} entry blocker and a potent immunomodulator, and could be useful for the treatment of autoimmune diseases and chronic inflammation. Furthermore, YM-58483 would be a candidate for the study of capacitative Ca^{2+} entry mechanisms through SOC/CRAC channels and for identification of putative Ca^{2+} channel genes.

PMID: 12707319 [PubMed - indexed for MEDLINE]

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